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[Intervention Review]

Ephedrine for myasthenia gravis, neonatal myasthenia and the congenital myasthenic syndromes

Charlotte Vrinten¹, Angeli M van der Zwaag¹, Stephanie S Weinreich¹, Rob JPM Scholten², Jan JGM Verschuuren³

¹Community Genetics Section, Clinical Genetics, VU University Medical Center, Amsterdam, Netherlands. ²Dutch Cochrane Centre, Julius Center for Health Sciences and Primary Care / University Medical Center Utrecht, Utrecht, Netherlands. ³Department of Neurology, Leiden University Medical Center, Leiden, Netherlands

Contact address: Stephanie S Weinreich, Community Genetics Section, Clinical Genetics, VU University Medical Center, BS7, D450, PO Box 7057, Amsterdam, 1007 MB, Netherlands. S.Weinreich@VUmc.nl.

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ABSTRACT

Background

Myasthenia is a condition in which neuromuscular transmission is affected by antibodies against neuromuscular junction components (autoimmune myasthenia gravis, MG; and neonatal myasthenia gravis, NMG) or by defects in genes for neuromuscular junction proteins (congenital myasthenic syndromes, CMSs). Clinically, some individuals seem to benefit from treatment with ephedrine, but its effects and adverse effects have not been systematically evaluated.

Objectives

To assess the effects and adverse effects of ephedrine in people with autoimmune MG, transient neonatal MG, and the congenital myasthenic syndromes.

Search methods

On 17 November 2014, we searched the Cochrane Neuromuscular Disease Group Specialized Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE. We also searched reference lists of articles, conference proceedings of relevant conferences, and prospective trial registers. In addition, we contacted manufacturers and researchers in the field.

Selection criteria

We considered randomised controlled trials (RCTs) and quasi-RCTs comparing ephedrine as a single or add-on treatment with any other active treatment, placebo, or no treatment in adults or children with autoimmune MG, NMG, or CMSs.

Data collection and analysis

Two review authors independently assessed study design and quality, and extracted data. We contacted study authors for additional information. We collected information on adverse effects from included articles, and contacted authors.

Main results

We found no RCTs or quasi-RCTs, and therefore could not establish the effect of ephedrine on MG, NMG and CMSs. We describe the results of 53 non-randomised studies narratively in the Discussion section, including observations of endurance, muscle strength and quality of life. Effects may differ depending on the type of myasthenia. Thirty-seven studies were in participants with CMS, five in participants with

MG, and in 11 the precise form of myasthenia was unknown. We found no studies for NMG. Reported adverse effects included tachycardia, sleep disturbances, nervousness, and withdrawal symptoms.

Authors' conclusions

There was no evidence available from RCTs or quasi-RCTs, but some observations from non-randomised studies are available. There is a need for more evidence from suitable forms of prospective RCTs, such as series of n-of-one RCTs, that use appropriate and validated outcome measures.

PLAIN LANGUAGE SUMMARY

Ephedrine treatment for myasthenia gravis, neonatal myasthenia and congenital myasthenic syndromes

Review question

We reviewed the evidence about the effect of ephedrine in adults and children with myasthenia gravis (MG), neonatal myasthenia and the congenital myasthenic syndromes (CMSs).

Background

Myasthenia is a group of rare conditions in which muscle fatigue and weakness are the main symptoms. These symptoms occur because signals do not pass from the nerve to the muscle properly. In autoimmune MG and neonatal myasthenia, the person's own immune system attacks the proteins that carry these signals. In CMS, there are inborn defects in these proteins. Most people with myasthenia respond well to standard drug and supportive treatments. Ephedrine could have a role when initial treatment is not successful. Ephedrine is a stimulating drug, although exactly how it works is unknown. As far as we know, the use of ephedrine has never been properly assessed in people with myasthenia.

Key results and quality of the evidence

Randomised studies provide the best quality evidence. We did not find any randomised studies of ephedrine in neonatal myasthenia, autoimmune MG, or the CMSs. Fifty-three non-randomised studies, which provide weaker evidence than randomised studies, have reported the effects of ephedrine on muscle weakness, fatigue, and quality of life. We have described these findings narratively in the Discussion section of the review. Effects may differ depending on the type of myasthenia. Adverse effects that were reported in these studies included palpitations, sleep disturbances, nervousness, and irritability when ephedrine was stopped. We conclude that there is a need for high-quality studies to assess the effects of ephedrine in MG, neonatal myasthenia, and the CMSs.

The evidence is current to November 2014.

BACKGROUND

Description of the condition

Myasthenia is a condition in which neuromuscular transmission is affected due either to antibodies against neuromuscular junction components (myasthenia gravis and neonatal myasthenia gravis), or to defects in any of the various genes that encode for neuromuscular junction proteins (congenital myasthenic syndromes, CMSs). The antibody-mediated form can be subdivided into autoimmune (childhood or adult onset) myasthenia gravis (MG), and transient neonatal myasthenia gravis (NMG), which is caused by a passive transfer of antibodies from a mother with autoimmune MG to her child. In this review, we considered treatment with ephedrine for all of these types of myasthenia. Each type is briefly described in the following paragraphs.

Autoimmune myasthenia gravis

Autoimmune MG is a rare disorder with a prevalence of 60 to 200 per million and an annual incidence of four to six per million (Juel 2007; Meyer 2010; Wirtz 2003). Eighty to 90 per cent of people with autoimmune MG produce autoantibodies directed against the acetylcholine receptor of the motor endplate (AChR MG) (Keeseey 2004; Meyer 2010). About five per cent of those with autoimmune MG have autoantibodies directed against the muscle-specific tyrosine kinase receptor of the motor endplate (MuSK MG) (Drachman 1994; Hoch 2001; Vincent 2003). Finally, some people have autoantibodies against Lrp4 (Higuchi 2011; Pevzner 2012; Zhang 2012). These are considered 'seropositive' for AChR, MuSK, or Lrp4 antibodies. A minority of those affected are seronegative; they lack antibodies against AChR or MuSK as measured by standard assays. However, in seronegative people, low titre antibodies to *clustered* acetylcholine receptors can sometimes be detected using cell-based assays (Leite 2008). Ten to 15 per cent of people with AChR MG have underlying thymoma (Keeseey 2004; Wirtz 2003). Symptoms of autoimmune MG include muscle fatigability and fluctuating muscle weakness in cranial and skeletal muscles. Therapy consists of treatment with an acetylcholinesterase inhibitor (AChEI), or immunosuppressive or immunomodulatory treatment to diminish the effect of the autoantibodies. Surgical treatment for autoimmune MG consists of thymectomy. The benefits of this procedure in people with non-thymoma MG have not been established conclusively (Juel 2007; Keeseey 2004; Meyer 2010). An international trial is ongoing (NCT00294658) and a published Cochrane systematic review on thymectomy for non-thymomatous myasthenia gravis will be updated once this evidence is available (Cea 2013). Treatment of autoimmune MG with AChEIs (Mehndiratta 2014), corticosteroids (Schneider-Gold 2005), immunosuppressive agents (Hart 2007), intravenous immunoglobulin (IVIg) (Gajdos 2012) and plasma exchange (Gajdos 2002) have been reviewed elsewhere.

(Transient) neonatal myasthenia gravis

Transient neonatal myasthenia gravis (NMG) is caused by maternal autoantibodies that are passively transferred from a mother with autoimmune MG to her child. Neonatal myasthenia gravis occurs in 10% to 20% of the newborns of mothers with autoimmune MG (Djelmis 2002; Evoli 2010). The annual incidence is unknown (Papazian 1992). Symptoms usually begin several hours after birth and include hypotonia and weakness, resulting in respiratory distress, poor suck and cry, and difficulty swallowing (Djelmis 2002; Evoli 2010). More severe cases present with foetal polyhydramnios

(excess of amniotic fluid in the amniotic sac) and congenital arthrogryposis multiplex (congenital contractures of multiple joints), followed by hypotonia and weakness (Chiezza 2011; Evoli 2010; Klehmet 2010; Papazian 1992; Plauché 1991). Treatment is supportive and usually consists of AChEIs, small frequent feedings and respiratory support, if necessary (Papazian 1992; Plauché 1991). Ninety per cent of affected newborns recover completely within weeks to months. Permanent symptoms have only been reported in rare cases (Papazian 1992).

Congenital myasthenic syndromes

The congenital myasthenic syndromes (CMSs) are a heterogeneous group of diseases caused by mutations in genes that encode for proteins that are essential in neuromuscular transmission. The combined prevalence of CMSs is one to two people per 500,000 (Eymard 2007). The syndromes can be divided into three subclasses: presynaptic, synaptic and post-synaptic, according to where in the neuromuscular junction the mutated gene is expressed (Barišić 2011; Engel 2012). Mutations are known in roughly 50% to 70% of those diagnosed with CMS (Eymard 2007; Kinali 2008). Symptoms include fatigability and weakness of limb-girdle muscles, and weakness of ocular, facial and bulbar muscles (Abicht 2003; Eymard 2007; Schara 2008). Respiratory difficulty may be present in severe cases (Abicht 2003; Barišić 2011). Foetal manifestations include arthrogryposis multiplex congenita and polyhydramnios (Eymard 2007). The first symptoms, if not present at birth, usually appear within the first year of life, but sometimes at a later age, or even in adulthood (Eymard 2007; Palace 2008). The diagnosis is based on familial occurrence, clinical findings, early onset, and on determining the specific type of syndrome. This can be done using electromyography, the response to AChEIs, studies of muscle endplate morphology, and molecular genetic testing (Abicht 2003; Eymard 2007; Kinali 2008). In contrast to autoimmune MG, CMSs are not due to autoantibodies, and immunomodulating therapies are therefore not effective. Pharmacological treatment of the CMS varies by syndrome, but usually consists of an AChEI, 3,4-diaminopyridine (3,4-DAP), ephedrine, albuterol, or a combination of these (Barišić 2011; Liewluck 2011; Sadeh 2011; Schara 2008). Non-pharmacological treatments include physiotherapy, gastric tube for feeding (if needed), close monitoring of respiratory and bulbar functions and, when necessary, respiratory support. Genetic counselling and prenatal diagnosis may also be warranted (Barišić 2011; Schara 2008). The prognosis is variable and for most CMS subtypes, cases ranging from mild to severe have been reported (Schara 2008).

Description of the intervention

The initial treatment for people with most forms of myasthenia consists of AChEIs or 3,4-DAP, or both. Some who do not respond well to these treatments seem to benefit from (add-on) treatment with ephedrine, for example, those with certain CMSs (Engel 2007; Lashley 2010). Ephedrine as a sulphate tablet is generally taken orally. Typical doses in adults are 25 mg twice daily. The dosage for children is 0.5 to 3 mg/kg/day divided over several doses, but doses of 150 to 200 mg per day are sometimes necessary (Bestue-Cardiel 2005; Engel 2007; Lashley 2010). Ephedrine is rapidly absorbed. It is partially metabolised to norephedrine in the liver, but is mainly excreted in the urine unchanged (Csajka 2005). The renal clearance is dependent on urine pH. Mean plasma half-life is approximately six hours and ranges from three to 11 hours (Csajka 2005; Wockhardt 2008). The most common

side effects are tachycardia (rapid heart rate), anxiety, nausea, restlessness and insomnia. In children, ephedrine may stimulate nocturnal enuresis, sleeplessness, or sometimes sedation (Lashley 2010; Wockhardt 2008). Contraindications for ephedrine are renal insufficiency, hypertension and certain cardiac diseases, such as long QT syndrome and angina pectoris (Csajka 2005; Wockhardt 2008). Unlike AChEIs or 3,4-DAP, there are currently no indications that ephedrine may worsen symptoms in certain subtypes of the CMS (Barišić 2011).

How the intervention might work

Ephedrine is a sympathomimetic agent which mainly affects the adrenergic receptors (Wockhardt 2008). Its beneficial effects in people with autoimmune MG have long been recognised (Boothby 1934; Edgeworth 1930; Edgeworth 1933). However, treatment with ephedrine has fallen into disuse after reports appeared of an increased risk of adverse cardiovascular and central nervous system events (stroke) associated with dietary supplements containing ephedra alkaloids, such as ephedrine and pseudoephedrine, and appetite suppressants containing norephedrine or phenylpropanolamine (Haller 2000; Kernan 2000). It has never been conclusively established that this is also the case for pharmaceutical preparations containing only ephedrine in doses used in the treatment of MG or any other registered indication for ephedrine-containing products (Ernst 2001). Recently, interest has increased in ephedrine as treatment for CMS, particularly DOK7 CMS (Bestue-Cardiel 2005 ; Lashley 2010 ; Schara 2009). Its mechanism of action in MG has been investigated (Gallagher 1979; Milone 1996; Shinnick-Gallagher 1979; Sieb 1993), but is not well understood (Engel 2007; Lashley 2010). For example, Sieb and Engel measured the effects of different concentrations of ephedrine on the muscle endplate in an in vitro canine model using microelectrode techniques. Ephedrine increased the quantal content of the endplate potential as well as the probability of quantal release, but at concentrations that would not be reached in those treated (Sieb 1993). Ephedrine might improve muscular transmission by stimulating β_2 -adrenergic receptors, as well as by partially stabilising the structure of the neuromuscular junction (Lashley 2010).

Why it is important to do this review

Ephedrine is a drug that is only used by a small number of people with myasthenia. Clinically, these people seem to benefit from this drug (Lashley 2010). However, its cost is not always reimbursed by health insurance companies due to a perceived lack of scientific evidence for efficacy. Furthermore, ephedrine is a methamphetamine analogue and can be used as a precursor in the (illegal) production of methamphetamine (MHRA 2012; UNODC 1988). It has been registered as a precursor drug in the United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances (UNODC 1988). Thus, the import and distribution of ephedrine is strictly regulated, which can jeopardise its availability for medicinal use (DEA 2010; Lashley 2010; UNODC 1988). This is especially true for people with myasthenia, because it is not a registered indication. For example, no ephedrine preparation is currently registered for marketing approval in humans in the European Union (EU) (EMA 2014), and pharmacies must either import the tablets from outside the EU or prepare the ephedrine sulphate tablets themselves.

OBJECTIVES

To assess the effects and adverse effects of ephedrine in people with autoimmune MG, transient neonatal MG, and the congenital myasthenic syndromes.

METHODS

Criteria for considering studies for this review

Types of studies

We considered randomised controlled trials (RCTs) and quasi-RCTs. Where no evidence from RCTs or quasi-RCTs was available, we summarised the results of non-randomised studies in the 'Discussion' section of this review.

Types of participants

We considered studies of adults and children with a diagnosis of myasthenia gravis (MG), neonatal myasthenia gravis (NMG) or congenital myasthenic syndromes (CMSs), based on clinical presentation, and electromyographic, immunological or genetic tests. Where no data on electromyographic, immunological or genetic tests were available, participants were included under the heading 'not genetically characterised CMS' (in the case of CMS) or 'unknown form of myasthenia' (all other cases).

Types of interventions

We considered any RCT or quasi-RCT that compared the effects of ephedrine as single treatment or as add-on treatment with any other active treatment, placebo, or no treatment. For the non-randomised studies, we included all studies that described the effect of ephedrine as single or add-on treatment.

Types of outcome measures

Primary outcomes

Change in a score measuring endurance within one to 14 days of the start of treatment, preferably measured by a recognised and validated instrument, such as the Quantitative Myasthenia Gravis Scale (QMG).

Secondary outcomes

1. Change in a score measuring endurance more than 14 days after the start of treatment, preferably measured by a recognised and validated instrument, such as the QMG.
2. Change in a score measuring muscle strength, preferably measured by a recognised and validated instrument, such as the Manual Muscle Test (MMT), within one to 14 days and more than 14 days after the start of treatment.
3. Change in a score measuring quality of life, preferably measured by a validated instrument (e.g. MG-QOL15) within one to 14 days and more than 14 days after the start of treatment.
4. Post-intervention Myasthenia Gravis Foundation of America (MGFA) status more than 14 days after the start of treatment.
5. Adverse events.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Neuromuscular Disease Group Specialised Register (17 November 2014), Cochrane Central Register of Controlled Trials (CENTRAL) (2014, Issue 10 in *The Cochrane Library*), MEDLINE (January 1966 to March 2013) and EMBASE (January 1980 to March 2013). We did not use a filter to identify RCTs and quasi-RCTs. The detailed search strategies are listed in the appendices: [Appendix 1](#) (MEDLINE), [Appendix 2](#) (EMBASE), [Appendix 3](#) (CENTRAL) and [Appendix 4](#) (Cochrane Neuromuscular Disease Group Specialized Register).

We scanned conference abstracts of the following conferences of the last 10 years for relevant studies, insofar as they were digitally available: International Congress on Neuromuscular Diseases (ICNMD), Peripheral Nerve Society, European Neurological Society, American Society of Human Genetics, European Society of Human Genetics, European Federation of Neurological Societies, European Congress of Immunology, International Congress of Neuroimmunology, World Muscle Society, American Academy of Neurology, Dutch Society for Immunology, International Congress of Myology, International Conference on Myasthenia Gravis and Related Disorders, World Congress of Neurology, Federation of European Neuroscience Societies, TREAT-NMD international conference, Dutch Endo-Neuro-Psycho meeting, New Directions in Biology and Disease of Skeletal Muscle Conference. We searched prospective trial registers using the online International Clinical Trials Registry Platform (ICTRP).

Searching other resources

We checked all references in the publications thus identified and contacted authors to identify any additional published or unpublished data. We aimed to contact any commercial manufacturers of ephedrine sulphate to ask about any study results on the efficacy of ephedrine for MG, NMG and CMS, but we did not identify any commercial manufacturers.

Data collection and analysis

Selection of studies

Two review authors (CV and AZ) independently screened titles and abstracts of the publications identified through the searches in an unblinded manner to assess eligibility for inclusion in this review. Where necessary, we examined the full-text publication. We excluded studies that did not meet the inclusion criteria described above. We resolved disagreements between review authors by discussion, by referral to a third review author (JV), or both. In the case of publications of studies in languages other than English, Dutch, German, French, Spanish or Italian, a native speaker assessed eligibility and performed the data extraction.

Data extraction and management

Two review authors (AZ and SW) independently extracted characteristics of each study using a standardised data extraction

form. A third author (CV) then checked the results. Extracted data included:

- study characteristics, including study design features, setting and funding source;
- characteristics of trial participants: inclusion and exclusion criteria, number of participants, gender and age distribution, how the diagnosis was established, severity and duration of disease;
- characteristics of the intervention: sample size, type, dose, frequency, route of administration and duration of treatment;
- characteristics of the outcome measures: measurement instruments used, features of these instruments (for example, the range of a scale and whether a high or a low score indicates a favourable outcome) and definitions of cut-off points (where appropriate);
- risk of bias (see below).

To determine the design of each study, we used the checklist developed by the 'Non-Randomised Studies Methods Group', which is described in Chapter 13 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Reeves 2011). For adverse events, we would have extracted the methods which were used for monitoring these events (for example, spontaneous reporting, participant checklist or diary), how these were reported (for example, whether any participants were excluded from the adverse events analysis), and the duration of follow-up (Loke 2011), but these characteristics were seldom reported. Where necessary, we contacted study authors to obtain further information.

Data synthesis

Because there was no evidence available from RCTs or quasi-RCTs, we described results from non-randomised studies narratively. The analysis methods we would have used for RCTs or quasi-RCTs are described in [Appendix 5](#).

RESULTS

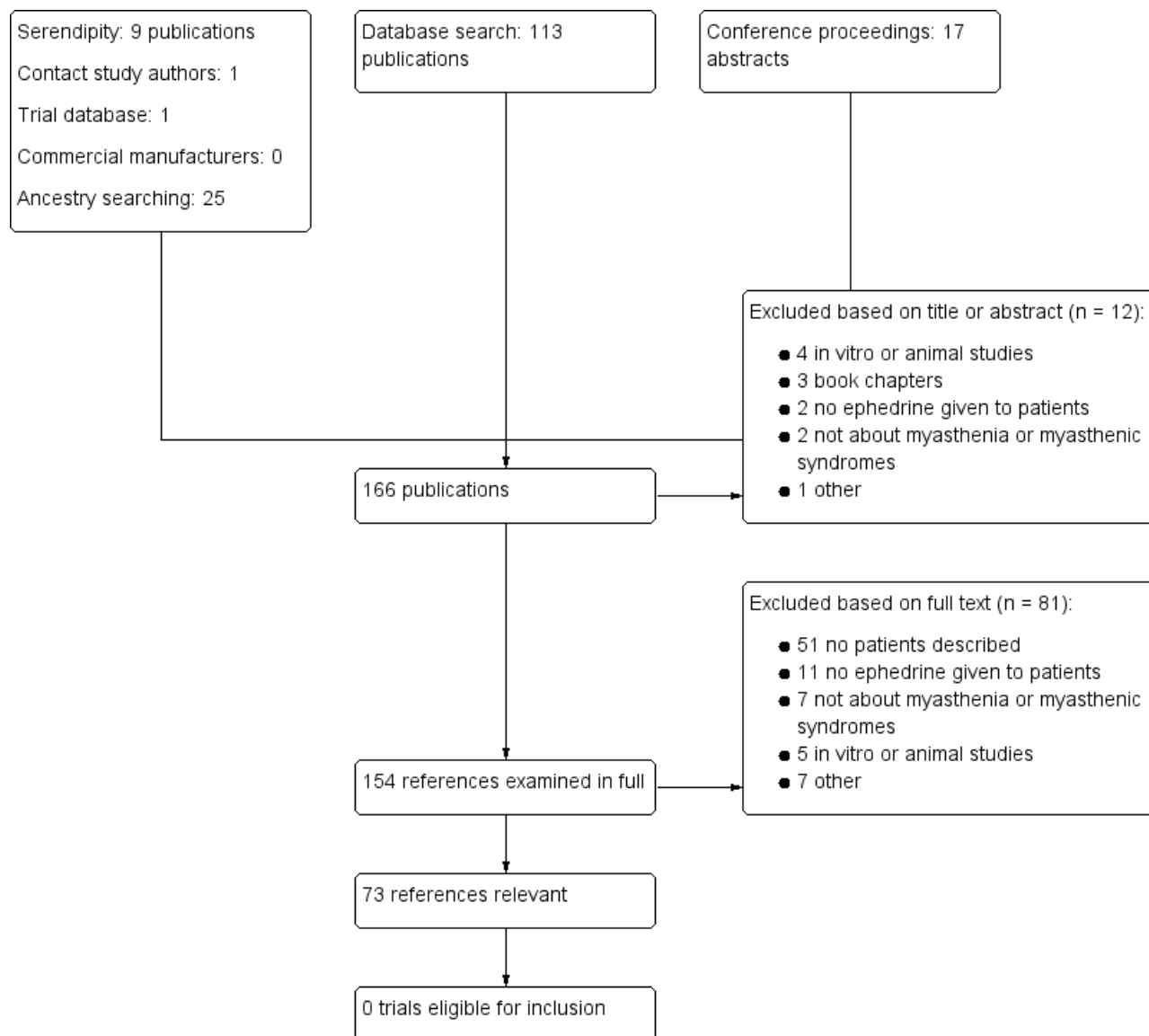
Description of studies

Results of the search

Our search resulted in 140 potentially eligible articles. After removal of duplicates, 113 articles remained. We identified a further 17 conference abstracts. Going through the reference lists of retrieved papers resulted in another 25 possibly relevant publications. We found nine references by a serendipitous search of ScienceDirect. Contacting authors of relevant papers resulted in one more reference being identified. We found one reference for an ongoing cross-over RCT for ephedrine in CMS due to mutations in the COLQ gene (NCT00541216).

We excluded 12 publications based on the title or abstract alone. We retrieved 154 references in full text to determine eligibility, which resulted in a further 81 references being excluded. We further processed the remaining 73 references. A flow diagram of the inclusion process is presented in [Figure 1](#).

Figure 1. Study flow diagram (a supplementary search shortly before publication resulted in 16 references, no RCTs or quasi-RCTs and seven additional studies to be assessed for inclusion in the Discussion at the next update).



We updated the search shortly before publication and identified no RCTs or quasi-RCTs. We identified seven additional studies to assess for inclusion in the Discussion at the next update ([Duran 2013](#); [Eymard 2013](#); [Hantai 2013](#); [Klein 2013](#); [Lorenzoni 2013](#); [Nicole 2014](#); [Witting 2014](#)).

Included studies

We did not identify any publications of RCTs or quasi-RCTs which investigated the effect of ephedrine on MG, NMG, or any of the CMSs. However, we identified 73 references of non-randomised studies and describe them in the [Discussion](#) section. Five of these are on myasthenia gravis (2 MuSK MG, 3 AChR MG) and 52 on CMS. The exact type of myasthenia could not be determined in a further 16 publications, mainly because these were older papers from before current diagnostic methods became available. These papers are therefore discussed separately (see 'Unknown form

of myasthenia' below). We identified no papers on the effects of ephedrine in NMG.

In total, the 73 publications describe 53 different non-randomised studies: six before-and-after studies (five CMS, one 'unknown form'), 29 case series (22 CMS, seven 'unknown form') and 18 case reports (five MG, 10 CMS, three 'unknown form'). The ongoing clinical trial that was identified was described as a cross-over RCT, but thus far results have only partially been published in the form of a case report, which we cover in this review. Some case series included people with different types of CMS. In these cases, the results for each type of CMS are discussed separately under the appropriate headings in the [Discussion](#). Only those people in each case series who were treated with ephedrine are included in the descriptions of the publications below. A summary of the findings is presented in [Table 1](#).

Risk of bias in included studies

Because we include no RCTs or quasi-RCTs, we have not carried out a formal assessment of risk of bias. We assume a high risk of bias (according to the Cochrane 'Risk of bias' tool) for all non-randomised studies.

Effects of interventions

Due to a lack of RCTs or quasi-RCTs, we could not establish the effect of ephedrine on MG, NMG and CMSs.

DISCUSSION

Our search did not identify any randomised controlled trials (RCTs) or quasi-RCTs, and therefore the results of non-randomised studies are described here, as per protocol (Vrinten 2012). The update of our search shortly before publication resulted in seven additional studies that are awaiting assessment for inclusion in the Discussion at the next update (Duran 2013; Eymard 2013; Hantai 2013; Klein 2013; Lorenzoni 2013; Nicole 2014; Witting 2014).

Autoimmune myasthenia gravis

AChR MG

Three case reports described the effects of ephedrine in people with AChR myasthenia gravis (MG) (Hashimoto 1981; Macdonald 1984; McAlpine 1988). All received ephedrine 15 to 40 mg four times daily orally in combination with pyridostigmine or with pyridostigmine and neostigmine. Muscle strength improved in two individuals (Hashimoto 1981; Macdonald 1984) and in one person symptoms were "well controlled" (McAlpine 1988). In one person, ephedrine was withdrawn preoperatively and started again postoperatively without any signs of increased muscle fatigue (Macdonald 1984). An intravenous injection of 4 mg ephedrine reversed ptosis "immediately" in one person before she was put on oral medication (Hashimoto 1981).

One person, who had experienced an unexplained psychotic episode several years earlier, developed psychotic symptoms (delusion of persecution) several weeks after ephedrine was started (Hashimoto 1981). This latest psychotic episode was attributed to treatment with ephedrine, which has a stimulatory effect on the central nervous system. The psychotic symptoms almost completely resolved after withdrawal of ephedrine.

MuSK MG

Two case reports described the effects of ephedrine in MuSK MG (Ehler 2008; Haran 2013). One person was treated with ephedrine, prednisone and azathioprine. This person had "slight vegetative complaints" after the first two days of ephedrine, but the dose could gradually be increased to 50 mg three times daily, which was well-tolerated and caused myasthenic symptoms to stabilise (Ehler 2008). The other person worsened on standard treatment, but her endurance level improved and her need for respiratory support decreased when salbutamol was given. She improved even further after substitution of salbutamol with a "longer acting beta-agonist" and 12 mg ephedrine three times daily (Haran 2013).

Neonatal myasthenia gravis

We did not identify any publications on the effects of ephedrine in neonatal myasthenia gravis.

Congenital myasthenic syndromes (CMSs)

Presynaptic CMS

CHAT

We identified a case series of 46 people, 10 of whom had been treated with ephedrine (Kinali 2008). One of these 10 had a CMS based on a mutation in CHAT (MIM ID: *118490; this person was also reported by Robb 2010 in a workshop report). Ephedrine in combination with pyridostigmine led to symptom improvement in this person. No adverse effects were reported.

Genetically uncharacterised presynaptic CMS

Maselli 2001 (also in Engel 2003) described a case series of three people with genetically uncharacterised presynaptic CMS. One of them was treated with ephedrine and pyridostigmine, which resulted in slight improvements in muscle strength and fatigability.

Synaptic CMS

AGRN

We identified two case series describing a total of three people with CMS due to mutations in AGRN who received ephedrine (MIM ID: *103320; one case was presented by B Eymard in Chaouch 2012; Huzé 2009). Two adult siblings received ephedrine 50 mg/day for three days and then 2 mg/kg each morning, which led to improvements in muscle strength, endurance, and general well-being (Huzé 2009). In contrast, ephedrine had resulted in "little change to her neuromuscular weakness" in a third person in whom it had recently been started (Chaouch 2012).

COLQ

Results of an ongoing trial and treatment results of 29 people with CMS due to mutations in COLQ (MIM ID* 603033) who were treated with ephedrine were described in one case report (Edvardson 2007; NCT00541216) and nine case series (Adamovičová 2012; Bestue-Cardiel 2005, also described in Bestué 2006, Brengman 2006, and Engel 2008; Chillingworth 2009; one case series presented by S Robb in Chaouch 2012; Wargon 2012, also described in Wargon 2011 and Bauduin 2011; Guven 2012; Kinali 2008; Mihaylova 2008a, also described in Mihaylova 2008b, Mihaylova 2008c and Chaouch 2012; and Yeung 2010). Reported dosages of ephedrine ranged from 50 to 200 mg/day divided over several doses for adults (Bestue-Cardiel 2005; Bestué 2006; Brengman 2006; Engel 2008; Edvardson 2007; Guven 2012; Mihaylova 2008c; Yeung 2010) and 0.5 to 1 mg/kg/day in combination with pyridostigmine (Guven 2012) or 2 to 5 mg/kg/day without pyridostigmine in children (Adamovičová 2012; Chaouch 2012; Mihaylova 2008c).

Seventeen people experienced improvements in endurance or muscle strength or both, such as walking distance and timed arm raise (Bauduin 2011; Bestue-Cardiel 2005; Bestué 2006; Brengman 2006; Chillingworth 2009; Edvardson 2007; Engel 2008; Mihaylova 2008a, Mihaylova 2008b, Mihaylova 2008c, Chaouch 2012; Wargon 2011; Wargon 2012; Yeung 2010).

Quality of life also seemed to improve in a number of people, although this was not assessed by validated instruments. Some striking anecdotes were reported, however. For example, one person who was previously unable to walk 200 metres without resting became able to play soccer and became a "normally active teenager" after ephedrine treatment was started (Bestue-

Cardiel 2005). Another became "independent in activities of daily living" (Yeung 2010). A third experienced a "resolution of dysphonia and dysphagia" and went from being wheelchair-dependent to needing only a crutch for mobility indoors (Wargon 2012).

In addition, several people experienced improvements in respiration, with reports of reduced needs for assisted ventilation (Wargon 2012), allowing weaning off ventilation altogether (Bauduin 2011), or improvements in spirometry measures (Edvardson 2007; Mihaylova 2008c; Yeung 2010).

Treatment with ephedrine was described as being "beneficial" in published results of a further five people (Adamovičová 2012; Kinali 2008) and in seven people who started ephedrine treatment as part of an ongoing trial (NCT00541216, personal communication), but details of treatment effects were not provided. Three people did not benefit from ephedrine (Chillingworth 2009; Guven 2012) and the results of treatment were not described in two people (Chaouch 2012).

Of note, Chillingworth 2009 described two siblings with the same genetic mutation and a similar phenotype, but different responses to ephedrine. One responded well, while the other's response was "disappointing". In contrast, Yeung 2010 reported two siblings with the same genetic mutation, but different phenotypes, who both seemed to benefit from ephedrine, although not to the same extent.

Not all studies reported whether there were adverse effects of treatment. However, no major adverse effects were seen in three people (Bestue-Cardiel 2005, personal communication; Yeung 2010). One person experienced "transient side effects" on higher doses of ephedrine (Chillingworth 2009) and two people experienced tachycardia, which led to the decision to discontinue ephedrine after one week in one person (Edvardson 2007; Guven 2012). One person had used ephedrine for 20 years before it was discontinued at age 37. She showed no response to ephedrine when it was started again at age 60 (Bestue-Cardiel 2005).

LAMB2

One case report (Maselli 2009) described the effect of ephedrine in a person with a CMS based on mutations in LAMB2 (MIM ID: *150325). The person went into respiratory crisis following a trial of anticholinesterases but "responded well" to ephedrine.

Postsynaptic CMS

CHRNAE

A total of 14 people with CMS caused by mutations in CHRNAE (MIM ID: *100725) were described in three case series (Beeson 2005; Burke 2004; Kinali 2008) and four case reports (Khan 2011; Linzoain 2011; Maselli 2011; Nogajski 2009). Most people received a combination of ephedrine and AChEIs (pyridostigmine) (Beeson 2005; Kinali 2008; Maselli 2011; Nogajski 2009). Two people received ephedrine (7.5 mg twice daily in one person) together with pyridostigmine and 3,4-DAP (Burke 2004; Linzoain 2011), and in one person together with neostigmine (Khan 2011).

Nine of 14 people showed a favourable response to ephedrine (Beeson 2005; Khan 2011; Kinali 2008; Linzoain 2011; Maselli 2011; Nogajski 2009). Swallowing time improved in three people (Beeson 2005). One person initially experienced improvements in fatigue, muscle strength, respiration, and chewing and swallowing (Linzoain 2011). However, this person's response

to ephedrine stabilised and then decreased again, leading to worsening of muscle strength and fatigue (Linzoain 2011; personal communication). Dose changes did not improve her condition at this point and it was discontinued. In contrast, other authors reported sustained responses over 1.5 and 10 years of follow-up in two people (Khan 2011; Nogajski 2009). Four people did not respond to treatment with ephedrine (Burke 2004). Treatment results were not reported for one person (Burke 2004). Adverse effects were not reported, but it was noted that one person was always very anxious after taking ephedrine, and a habituation or addiction syndrome was observed when ephedrine was discontinued in this person (Linzoain 2011; personal communication).

DOK7

Forty people with a CMS based on mutations in DOK7 (MIM ID: *610285) who received ephedrine were described in 19 publications of 12 studies, which included four before-and-after studies (Burke 2009; Lashley 2010, also described by J Palace in Chaouch 2012, and in Cossins 2010 and Lashley 2009; Schara 2009 and Schara 2007; Srour 2010), one case study (Schara 2012), and seven case series (Anderson 2008; Ben Ammar 2010 and Sarkozy 2010; Burke 2013 and Burke 2011; Della Marina 2011; Kinali 2008; Palace 2007; Selcen 2008; Slater 2006). Dosages varied between 7.5 and 100 mg/day (paediatric doses: 0.5 to 1.0 mg/kg/day), sometimes in combination with 3,4-DAP or pyridostigmine.

Endurance or muscle strength or both improved in 15 people, as measured by various tests, such as the two-minute walk test, QMG test, and timed arm and leg raise (Burke 2009; Burke 2013 and Burke 2011; Della Marina 2011; Lashley 2010, Chaouch 2012, Cossins 2010, and Lashley 2009; Schara 2012; Srour 2010). Quality of life (QOL) seemed to have improved in a similar number of people, although this was not assessed with validated outcome measures (Burke 2009; Della Marina 2011; Lashley 2010, Chaouch 2012, Cossins 2010, and Lashley 2009; Schara 2009 and Schara 2007). Some striking improvements in QOL were reported: many people became more independent and able to participate in school, work and social life (Schara 2009 and Schara 2007). One person had been unable to climb stairs in the evenings, but was unrestricted in activities of daily living after two years of treatment with ephedrine (Della Marina 2011). Another could do five squats before ephedrine was started, but was able to do 50 afterwards. A third person used to walk with crutches but was able to walk unassisted, go for jogs and do sit-ups after ephedrine was started, and a fourth had been using a wheelchair for longer distances but was now able to go on prolonged shopping trips and wear high heels (Lashley 2010). Treatment effects were described as "beneficial" in another 13 people, but no further details were given (Anderson 2008; Ben Ammar 2010 and Sarkozy 2010; Kinali 2008; Palace 2007 and Slater 2006; Selcen 2008). Four people did not benefit from ephedrine (Anderson 2008; Lashley 2010, Chaouch 2012, Cossins 2010, and Lashley 2009).

Adverse effects were reported in a quarter of people (10 of 40), including tachycardia (two people), epistaxis (two people), sleep disturbances (two people), muscle cramps, sweating, nervous feeling, cold extremities, dry mouth and hypertension (Burke 2009; Lashley 2010, Chaouch 2012, Cossins 2010, and Lashley 2009; Schara 2009 and Schara 2007; and Srour 2010, personal communication). One person experienced a habituation of beneficial effects after 22 months and a dose increase led to

unacceptable adverse effects. For three people, adverse effects were the reason to discontinue ephedrine. The others rated their adverse effects as minimal compared to the beneficial effects of ephedrine. Ephedrine was replaced by salbutamol in two people because of adverse effects in one person (Srouf 2010) and for "parental convenience" in the other (Burke 2013 and Burke 2011). Finally, it is noteworthy that one before-and-after study used vital capacity and repetitive nerve stimulation (RNS) studies to evaluate the effects of ephedrine treatment, but the authors commented that these measures were inadequate to monitor the effects of treatment (Schara 2009 and Schara 2007).

Fast-channel syndromes

We identified one case series that described a single person with a fast channel CMS who received ephedrine, possibly together with pyridostigmine and 3,4-DAP (Palace 2012). Ephedrine did not seem to have an effect. However, the authors state it may not have been tried for long enough for any benefit to become apparent before it was stopped again for reasons that were not reported.

Limb-girdle CMS

We identified three case series which described a total of five people with limb-girdle CMS who received ephedrine (presented by J Palace in Beeson 2005; Kinali 2008; Slater 2006). The last paper described the effects of ephedrine in four people, but one person was later found to have DOK7 CMS and was also described by Palace 2007. This individual was therefore not included here, but in the DOK7 section. All of the remaining five people responded favourably to ephedrine, including some who had failed to respond, or had deteriorated, on pyridostigmine.

MUSK

We found one case series (Mihaylova 2009) and one case report (Maselli 2010), which together described two people with CMS based on mutations in the MUSK gene (MIM ID: *601296) who received ephedrine. One person did not tolerate it and the other showed no response to ephedrine.

RAPSN

Three case series reported on four people with CMS based on mutations in RAPSN (MIM ID: *601592) who received ephedrine (Banwell 2004; Burke 2004; J Colomer in Chaouch 2012). Ephedrine doses were not reported, but all four people responded favourably. Two of the four were siblings, with compound heterozygous mutations in RAPSN and a heterozygous mutation in DOK7 (Chaouch 2012). They received ephedrine in combination with AChEIs and 3,4-DAP. Symptoms improved in both, but one sibling remained dependent on nocturnal ventilation. A third person's strength improved such that he was able to walk unassisted for the first time (Banwell 2004). Two people later switched to 3,4-DAP, which was better tolerated (Banwell 2004; Burke 2004).

Slow-channel syndromes

A single person with a slow-channel syndrome who received ephedrine was described in a case series of people with various types of CMS. This person showed a slight improvement (J Palace in Beeson 2005).

Not genetically characterised CMS

We identified two case series that partly described the same people (J Palace in Beeson 2005; Kinali 2008), one before-and-after study (Felice 1996), and one case report (Terblanche 2008) on the effects of ephedrine in genetically uncharacterised CMS. Altogether, they described the results of ephedrine in five people. The before-and-after study failed to find significant changes in forced vital capacity (FVC) and muscle strength (Medical Research Council (MRC) Scale) scores two hours after a single dose (25 to 50 mg, orally) or one week after treatment with ephedrine (25 mg twice daily, orally) in three people (Felice 1996). The per cent decrement during RNS studies remained unchanged two hours after 25 to 50 mg ephedrine orally or one week after 25 mg ephedrine twice daily orally. Similarly, the per cent decrement of the compound muscle action potential (CMAP) following 3-Hz RNS failed to change significantly 20, 40, or 60 minutes after 25 mg intramuscular (i.m.) ephedrine. However, all recipients described moderate subjective improvements in strength and stamina. Adverse effects included "mild" tachycardia after 50 mg oral and 25 mg i.m. ephedrine (Felice 1996). The effect of ephedrine was not described in detail in the other reports, but both people in these reports improved (Beeson 2005; Kinali 2008; Terblanche 2008).

Unknown form of myasthenia

Three case reports (Dalkara 1988; Nelson 1935; Yahr 1944), seven case series (Chan-Lui 1984; Edgeworth 1930, also described in Boothby 1934 and Edgeworth 1933; Patten 1972; Pearce 2005, also described in Johnston 2005, Walker 1934 and Walker 1935; Schwarz 1955; Simpson 1966; Viets 1939) and one before-and-after study (Wilson 1944) described a total of 196 people who were treated with ephedrine. Daily oral dosages of ephedrine ranged from 15 to 96 mg, usually divided over several doses, and given either alone or in combination with various other drugs, such as glycine, pyridostigmine, prednisolone, potassium salts, neostigmine, and ambenonium. Subcutaneous doses of up to 64 mg were reported, either alone or in combination with neostigmine (Wilson 1944). In one report, ephedrine was given as an eye drop solution of 3% (Dalkara 1988).

152 people improved when ephedrine was given, but no further details were reported (Boothby 1934; Patten 1972; Pearce 2005, Johnston 2005, Walker 1934 and Walker 1935; Schwarz 1955; Simpson 1966; Viets 1939). Twenty-eight people did not show a response (Boothby 1934; Pearce 2005, Johnston 2005, Walker 1934 and Walker 1935; Simpson 1966; Viets 1939; Yahr 1944), and one person worsened (Boothby 1934). Improvements in muscle strength were reported for two people by Edgeworth 1933 (also described in Edgeworth 1930 and Boothby 1934) and Nelson 1935. Furthermore, in the series of before-and-after trials in ten people conducted by Wilson 1944, a greater increase in muscle strength and longer duration of effect were observed when a subcutaneous injection of ephedrine was added to neostigmine, compared to neostigmine alone. However, in the majority of people muscle strength did not increase when an oral dose of ephedrine was added to oral neostigmine, although the effects of neostigmine did last longer (Wilson 1944). We identified two studies that solely investigated the effect of ephedrine on ocular symptoms (Chan-Lui 1984; Dalkara 1988). Ptosis and ophthalmoplegia responded poorly to ephedrine in two people (Chan-Lui 1984). Eye drops of 3% ephedrine solution resulted in an increased pupillary diameter in one person (Dalkara 1988).

In addition, several authors described attempts to decrease the dose of ephedrine, or to withdraw ephedrine altogether, to ascertain whether an observed effect was really due to ephedrine (Boothby 1934; Edgeworth 1930 and Edgeworth 1933; Nelson 1935; Patten 1972). Five people were able to decrease the dose of ephedrine without an increase in symptoms (Boothby 1934). Temporary withdrawal of ephedrine in three people resulted in an increase in muscle weakness, disability or both in all three (Edgeworth 1930 and Edgeworth 1933; Nelson 1935; Patten 1972).

Most studies did not describe adverse effects of ephedrine, but one study reported that a dose of more than 48 mg/day was not tolerated in one person (Boothby 1934, Edgeworth 1933, and Edgeworth 1930). Surprisingly, pre-existent tachycardia improved when ephedrine was given in the same person. One child died of unknown causes five days after glycine was added to ephedrine (Nelson 1935).

Summary of main results

Our literature search did not identify any RCTs or quasi-RCTs, but did identify a large number of non-randomised studies that describe the effects of ephedrine in autoimmune MG and the CMSs. Some of the reports date to the first half of the 20th century, illustrating that ephedrine has been used to treat myasthenic symptoms for almost a hundred years.

A wide range of doses was reported in these non-randomised studies. People usually received a total oral dose of 50 to 200 mg/day (adults) or 0.5 to 3.0 mg/kg/day (children) divided over several doses, although some benefited from much smaller doses, for example 7.5 or 16 mg/day. Ephedrine was often used in combination with other drugs, such as AChEIs, neostigmine, or 3,4-DAP.

We had aimed to include only results from RCTs or quasi-RCTs and describe the results of non-randomised studies in the Discussion if the results from RCTs or quasi-RCTs had left any knowledge gaps. However, our search did not identify any RCTs or quasi-RCTs and so we considered whether the results from the identified before-and-after studies could be evaluated according to the Cochrane Effective Practice and Organisation of Care (EPoC) guideline (EPoC 2013). This guideline describes which study designs, other than RCTs and non-randomised controlled trials, should be considered in a review of the effectiveness of a healthcare intervention. However, we decided that the included before-and-after studies could not be evaluated according to the EPoC guideline, because a control group or multiple measurements before and after the intervention were lacking. We therefore decided not to give primacy to the results of any one type of non-randomised study and summarised all non-randomised evidence. However, a high risk of bias should be assumed for the non-randomised studies presented here and no firm conclusions about the efficacy of ephedrine in autoimmune MG or CMSs can be drawn from this evidence.

Nevertheless, many of the included reports describe favourable effects of ephedrine on myasthenic symptoms (Table 1). Only some of the studies reported no effects or adverse effects, which led to the discontinuation of ephedrine in some people. Adverse effects were most commonly experienced in the first days or weeks after starting treatment with ephedrine, or after a dose increase. The adverse effect reported most often was tachycardia, but sleep disturbances, anxiety, and epistaxis were also reported. Some people showed

habituation to ephedrine, and one person experienced withdrawal symptoms.

Overall completeness and applicability of evidence

Despite the large number of non-randomised studies described in this review, many gaps in our knowledge remain. We have already noted that the results from the non-randomised studies should be interpreted with caution. In addition, we found a relatively large number of studies for some types of myasthenia (such as COLQ CMS and DOK7 CMS), while for others (such as autoimmune MG, AGRN CMS, or RAPSN CMS) only a small number of studies was available, or even only a single case report (e.g. LAMB2, fast-channel CMS, slow-channel CMS). Furthermore, it should be noted that selection for treatment with ephedrine may have been biased towards those who were likely to show a favourable response or who responded poorly to medications of first choice (confounding by indication). Because the studies were not prospective or controlled, information bias is also a risk. Publication bias may have occurred towards cases in which positive responses to ephedrine had been recorded, although the fact that the effectiveness of ephedrine was not the main topic of most studies makes it less likely that this occurred. For these various reasons, the results from non-randomised studies should be interpreted with caution.

Quality of the evidence

The quality of the evidence was low: we did not identify any RCTs or quasi-RCTs and all studies described in this review were non-randomised. In addition, reporting in these studies was often poor. First, many studies did not fully report on characteristics such as dose, frequency, and duration of ephedrine treatment, co-medication, and time points at which the effects of treatment were assessed. Secondly, recognised and validated outcome measures were rarely used, and outcomes were often described in imprecise and vague terms, which made comparisons across studies difficult. Finally, adverse effects were seldom included or adequately described.

Potential biases in the review process

We have attempted to minimise potential biases in the review process by having two review authors independently assess eligibility for inclusion (AZ and CV), by having two review authors (AZ and SW) conduct the data extraction independently, and by referring to a third review author (JV) to resolve any disagreements. Furthermore, to minimise language bias, we consulted native speakers during the data extraction process for publications in languages unfamiliar to the review authors.

Agreements and disagreements with other studies or reviews

To our knowledge, no prior systematic reviews about the effects of ephedrine in MG, NMG or CMSs have been conducted. However, our literature search identified a number of narrative reviews which discuss the general treatment of CMS, and some of these included the use of ephedrine. Several recent reviews state that ephedrine may be beneficial in people with DOK7 (Engel 2007; Engel 2012; Engel 2012a; Lorenzoni 2012; Palace 2008; Schara 2008), COLQ (Engel 2007; Engel 2012; Engel 2012a; Lorenzoni 2012; Palace 2008; Schara 2008), LAMB2 (Lorenzoni 2012), RAPSN (Engel 2007; Engel 2012; Engel 2012a), AGRN (Lorenzoni 2012), and slow-channel CMS (Palace 2008). Some of these reviews combine evidence available

from the literature with the clinical expertise of the review authors. We have included in this review all relevant references that were referred to by the authors of these reviews. However, in the present review, we deemed this evidence to be of insufficient quality either to support or to discourage the use of ephedrine for these syndromes.

AUTHORS' CONCLUSIONS

Implications for practice

No randomised controlled trials or quasi-randomised controlled trials have been conducted to determine the effects of ephedrine in myasthenia gravis, neonatal myasthenia gravis, or congenital myasthenic syndromes. Our search did not identify any non-randomised studies which described the effect of ephedrine in neonatal myasthenia gravis. Limited evidence is available from before-and-after studies, case series, and case reports, and suggests that there might be an effect of ephedrine on endurance, muscle strength, and quality of life in people with myasthenia gravis and some types of congenital myasthenic syndrome. Effects may depend on the type of myasthenia, however, and use of ephedrine may be limited by adverse effects such as tachycardia, sleep disturbances, nervousness, habituation effects, and withdrawal symptoms. Due to the high risk of bias, the results of these non-randomised studies should be interpreted with care.

Implications for research

In order to obtain valid and reliable estimates of the effects of ephedrine on myasthenic symptoms, it is necessary that prospective, blinded, randomised and controlled trials are conducted for the different types of myasthenia described in this review. Due to the rarity of many of the congenital myasthenic syndromes and the small numbers of people with myasthenia gravis who respond poorly to standard therapy and for whom treatment with ephedrine may thus be considered, it may prove unfeasible to conduct parallel group-randomised controlled trials, even on an international scale. Other types of randomised controlled trial should therefore be considered, such as randomised controlled cross-over trials or (series of) n-of-one randomised controlled trials. Moreover, more research is needed to establish which outcome measures should be used to determine the effects of treatment. Some studies included in this review (e.g. [Felice 1996](#); [Lashley 2010](#); [Schara 2009](#) and [Schara 2007](#)) described discrepancies between objective measures, such as forced vital capacity and electromyographic studies, and subjective measures of treatment effect, such as self-reported quality of life. This suggests that the objective outcome measures chosen in those studies may not have been optimal for recording any improvements in myasthenic symptoms, or alternatively that

the experienced beneficial effects of ephedrine may reflect an underlying placebo effect. Furthermore, more research is needed to establish the best time interval at which the outcomes should be measured. Some people with autoimmune myasthenia gravis or congenital myasthenic syndromes seem to respond to treatment with ephedrine within minutes or days ([Hashimoto 1981](#); [Wargon 2012](#)), but several authors have commented that it may take weeks or months for ephedrine to reach full effect ([Chaouch 2012](#); [Robb 2010](#)). Thus, the time interval for the outcome measures may need to be changed in future reviews to reflect these observations. It should be noted, however, that conducting trials to establish the efficacy of ephedrine may be hampered by the issues around the availability of ephedrine, as outlined in the [Background](#).

Blind, randomised, controlled studies of adequate duration and using well-chosen and standardised outcomes measured at appropriate intervals may help to establish the true effect of ephedrine on myasthenic symptoms for the different types of myasthenia. The search for valid and reliable estimates of the effect of ephedrine on myasthenic symptoms could be greatly facilitated by setting up an international database that allows all people with myasthenia who are treated with ephedrine to be registered and tracked over time. Such a register should include those people who did and did not benefit from ephedrine, those in whom it was discontinued (and why), and those who experienced adverse effects of ephedrine.

In summary, the studies included in this review suggest that ephedrine may improve muscle weakness and fatigue in some people with myasthenia gravis and in some types of congenital myasthenic syndrome, but scientifically sound and novel ways to validly and reliably estimate the effect of ephedrine in these rare conditions are needed.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of ongoing studies [ordered by study ID]

NCT00541216

Trial name or title	Ephedrine for the treatment of congenital myasthenia
Methods	Safety/efficacy study using a randomised, double-blind, placebo-controlled single cross-over design
Participants	Male or female COLQ patients
Interventions	Ephedrine (5 weeks) versus placebo (5 weeks)
Outcomes	Strength, fatigability, quality of life, spirometry
Starting date	October 2007
Contact information	Principal Investigator: Simon Edvardson Hadassah Medical Organization
Notes	Enrolment by invitation only

ADDITIONAL TABLES

Table 1. Summaries of findings of non-randomised studies

Type of myasthenia	Be-fore-af-ter	Case series	Case re-ports	No. of peo-ple	Ephedrine dose (orally, unless stated other-wise)	Effect
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Table 1. Summaries of findings of non-randomised studies *(Continued)*

	stud- ies		in re- view			
Autoimmune						
AChR MG (Hashimoto 1981; Macdonald 1984; McAlpine 1988)	-	-	3	3	15 to 40 mg 4 times daily or 4 mg I.V. Not reported in some.	Possible improvement in muscle strength in 3 people. Adverse effects reported.
MuSK MG (Ehler 2008; Haran 2013)	-	-	2	2	12 to 50 mg 3 times daily	Possible improvement in symptoms in 2 people. Adverse effects reported.
Neonatal myasthenia gravis						
	n/a	n/a	n/a	n/a	n/a	n/a
Congenital myasthenic syndromes						
Presynaptic						
CHAT (Kinali 2008 and Robb 2010)	-	1	-	1	Not reported	Possible improvement in symptoms in 1 person.
Presynaptic other (Engel 2003 and Maselli 2001)	-	1	-	1	Not reported	Possible improvement in muscle strength and fatigue in 1 person.
Synaptic						
AGRN (Chaouch 2012; Huzé 2009)	-	2	-	3	50 mg/day or 2 mg/kg/day	Possible improvements in muscle strength, endurance and well-being in 2 people. No change in 1 person.
COLQ (Adamovičová 2012; Bestue-Cardiel 2005, Bestué 2006, Brengman 2006 and Engel 2008; Chaouch 2012; Chillingworth 2009; Edvardson 2007 and NCT00541216; Guven 2012; Kinali 2008; Mihaylova 2008a, Mihaylova 2008b, Mihaylova 2008c and Chaouch 2012; Wargon 2012, Wargon	-	9	1	29	50 to 200 mg/day (adults) or 0.5 to 5 mg/kg/day (children). Not reported in some.	Possible improvements in endurance, muscle strength or both in about half of 29 people. Possible improvements in quality of life and respiration. No change reported in 3 people. Adverse effects reported.

Table 1. Summaries of findings of non-randomised studies (Continued)

2011 and Bauduin 2011; Yeung 2010)

LAMB2 (Maselli 2009)	-	-	1	1	Not reported	Possible improvements in 1 person.
<i>Postsynaptic</i>						
CHRNE (Beeson 2005; Burke 2004; Khan 2011; Kinali 2008; Linzoain 2011; Maselli 2011; Nogajski 2009)	-	3	4	14	7.5 mg twice daily. Not reported in most.	Possible improvements in 9/14 people. No change in 4 people. Adverse effects suspected.
DOK7 (Anderson 2008; Ben Amar 2010 and Sarkozy 2010; Burke 2009; Burke 2013 and Burke 2011; Della Marina 2011; Kinali 2008; Lashley 2010, Chaouch 2012, Cossins 2010 and Lashley 2009; Palace 2007 and Slater 2006; Schara 2009 and Schara 2007; Schara 2012; Selcen 2008; Srour 2010)	4	7	1	40	7.5 to 100 mg/day or 0.5 to 1.0 mg/kg/day (children). Not reported in some.	Possible improvements in endurance, muscle strength, quality of life, or unspecified improvements in majority of 40 people. No response in 4 people. Adverse effects reported in 10 people.
Fast channel (Palace 2012)	-	-	1	1	Not reported	Possibly no effect in 1 person.
Limb-girdle (Beeson 2005; Kinali 2008; Slater 2006)	-	3		5	Not reported	Possible improvements in all 5 people.
MuSK (Maselli 2010; Mihaylova 2009)	-	1	1	2	Not reported	No response in 1 person. Not tolerated in the other person.
RAPSN (Banwell 2004; Burke 2004; Chaouch 2012)	-	3		4	Not reported	Possible improvements in all 4 people.
Slow channel (Beeson 2005)	-	1	-	1	Not reported	Possible slight improvement in 1 person.
<i>Not genetically characterised CMS</i>						

Table 1. Summaries of findings of non-randomised studies (Continued)

(Beeson 2005; Felice 1996; Kinali 2008; Terblanche 2008)	1	2	1	5	25 - 50 mg oral, or 25 mg twice daily oral, or 25 mg I.M. Not reported in some.	No objective improvements in forced vital capacity, muscle strength, or RNS/CMAP decrement. Possible subjective improvements in strength. Adverse effects reported.
Unknown form of myasthenia						
(Chan-Lui 1984; Dalkara 1988; Edgeworth 1930, Edgeworth 1933 and Boothby 1934; Nelson 1935; Pat-ten 1972; Pearce 2005, Johnston 2005, Walker 1934 and Walker 1935; Schwarz 1955; Simpson 1966; Vi-ets 1939; Wilson 1944; Yahr 1944)	1	7	3	196	15 - 96 mg oral, or < 64 mg S.C., or 3% eye drop solution. Not re-ported in some.	Possible improvements in a majority of people. No response in a minority. Adverse effects reported.

AChR: acetylcholine receptor; CMAP: compound muscle action potential; CMS: congenital myasthenic syndrome; I.M.: intramuscular; I.V.: intravenous; MG: myasthenia gravis; MuSK: muscle specific tyrosine kinase; n/a: not applicable; RNS: repetitive nerve stimulation; S.C.: subcutaneous

APPENDICES

Appendix 1. MEDLINE (OvidSP) search strategy

Database: Ovid MEDLINE(R) <1946 to November Week 1 2014>

Search Strategy:

```

1 myastheni$.mp. (16285)
2 Ephedrine/ (4554)
3 exp Ephedra/ (427)
4 (biophedrin$ or efedra$ or ephedra$ or fedrin$ or efedrin$ or efidrin$ or ephedrin$ or Sal-phedrine$ or Salphedrine$ or sanedrin$ or zephrol$).mp. (6191)
5 or/2-4 (6191)
6 1 and 5 (60)
7 remove duplicates from 6 (49)

```

Appendix 2. EMBASE (OvidSP) search strategy

Database: Embase <1980 to 2014 Week 46>

Search Strategy:

```

1 myastheni*.mp. (20734)
2 ephedrine/ (10889)
3 (ephedrin$ or Sal-phedrine$ or salphedrine$ or biophedrin$ or efedra$ or ephedra$ or fedrin$ or efedrin$ or efidrin$ or sanedrin$ or zephrol$).mp. (13006)
4 2 or 3 (13006)
5 1 and 4 (123)
6 remove duplicates from 5 (122)

```

Appendix 3. CENTRAL search strategy

#1 myastheni*
 #2 MeSH descriptor Ephedra explode all trees
 #3 biophedrin* or efedra* or ephedra* or fedrin* or efedrin* or efidrin* or ephedrin* or Sal-phedrine* or Salphedrine* or sanedrin* or zephrol*
 #4 (#2 OR #3)
 #5 (#1 AND #4)

Appendix 4. Cochrane Neuromuscular Disease Group Specialized Register (CRS) search strategy

#1 myastheni* [REFERENCE] [STANDARD]
 #2 biophedrin* or efedra* or ephedra* or fedrin* or efedrin* or efidrin* or ephedrin* or Sal-phedrine* or Salphedrine* or sanedrin* or zephrol* [REFERENCE] [STANDARD]
 #3 #1 and #2 [REFERENCE] [STANDARD]

Appendix 5. Methods (quasi-)RCTs

Assessment of risk of bias in included studies

For RCTs or quasi-RCTs, two review authors (CV and SW) would have independently assessed risk of bias using the Cochrane Collaboration's 'Risk of bias' tool, as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* 5.1.0 ([Higgins 2011b](#)). This tool assesses risk of bias for the following domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other sources of bias, for example baseline imbalances. We would have summarised the assessment for each included trial in a 'Risk of bias' table as described in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011a](#)).

Measures of treatment effect

For continuous data from included trials, we would have taken the change in score from baseline to post-intervention as the main outcome of interest. We would have used the mean difference (MD) with a 95% confidence interval (CI) as the summary statistic.

For dichotomous data, we would have used the number of participants experiencing the event in each group and the number of participants in each group to calculate a risk ratio (RR) and risk difference (RD) with 95% CI.

Dealing with missing data

We would have contacted the principal study authors to obtain any missing data needed for the meta-analysis of RCTs or quasi-RCTs.

Assessment of heterogeneity

For RCTs or quasi-RCTs, we would have assessed heterogeneity of intervention effects by looking at the forest plot and by means of the Chi² statistic (P value) or the I² statistic. We would have taken a P value of less than .10 to indicate heterogeneity. We would have interpreted the I² statistic as follows:

- 0% to 40%: may not be important;
- 30% to 60%: there may be moderate heterogeneity;
- 50% to 90%: there may be substantial heterogeneity;
- 75% to 100%: there is considerable heterogeneity.

If included trials were small in sample size or few in number, we would have used visual inspection of the forest plot to assess heterogeneity. A possible reason for potential heterogeneity may be differences between autoimmune MG and CMS. Depending on whether a reasonable number of trials had been included, we would have explored heterogeneity using subgroup analyses as described below (in Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

Depending on whether a reasonable number of trials studies had been included in any one meta-analysis (at least 10), we would have created a funnel plot to examine the possibility of publication bias using the Review Manager 5 software of the Cochrane Collaboration ([RevMan 2014](#)).

Data synthesis

For RCTs or quasi-RCTs, we would have performed a meta-analysis of treatment effect in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* 5.1.0 ([Higgins 2011a](#)) using the Cochrane statistical package Review Manager 5 ([RevMan 2014](#)), if substantial or considerable heterogeneity was absent. We would have conducted separate meta-analyses for placebo-controlled studies and studies that used active controls. We would have used fixed-effect and random-effects methods as appropriate.

If meta-analysis was inappropriate, we would have described study features (including risk of bias assessment), results and main conclusions per included trial. Where no evidence was available from RCTs or quasi-RCTs, we described results from non-randomised studies narratively.

Subgroup analysis and investigation of heterogeneity

We would have explored sources of heterogeneity in the RCTs and quasi-RCTs. Depending on whether a reasonable number of studies per subgroup characteristic (at least 10) were available, we would have performed a meta-regression analysis to determine if a dose-response relationship for the primary outcome measure existed, and would have performed subgroup analyses for participants with autoimmune MG and participants with a genetically determined CMS.

Sensitivity analysis

For included trials, we would have explored the robustness of the results by performing the following sensitivity analyses, as recommended by the Cochrane Neuromuscular Disease Group:

- The analysis would have been repeated excluding unpublished data (if there was any);
- The analysis would have been repeated excluding studies of the lowest quality;
- The analysis would have been repeated excluding any very large studies;
- The analysis would have been repeated excluding other types of studies, depending on the degree to which there were choices about the inclusion and exclusion criteria.
- In the case of dichotomised ordinal data, we would have tested the robustness of the results by repeating the analysis using different cut-off points.

CONTRIBUTIONS OF AUTHORS

CV played the lead in writing the protocol and designing the review. She developed criteria for a search strategy in conjunction with the Trials Search Co-ordinator. Together with AZ, she searched the identified titles and abstracts and obtained copies of papers. She selected which studies to include together with AZ, and checked extracted data. She and AZ carried out the analysis of the results and interpreted the analysis together with SW. She entered data into Review Manager 5 and took the lead in drafting the final review.

AZ searched identified titles and abstracts, obtained full-text copies of relevant papers, and extracted data in conjunction with CV and SW. Together with CV, she conducted the analysis of the data, entered data into Review Manager 5, and drafted the Results, Discussion, and Conclusion sections.

SW conceived the review and secured funding. Together with AZ, she extracted data and helped to interpret the analysis, in preparation for discussions with RS and JV. She coached CV in drafting the final review with special attention to the consumer and policy perspectives. Together with JV she will update the review.

RS helped design the review and has provided general advice. He contributed to the interpretation of the analysis and to the draft of the final review, especially from a methodological perspective.

JV helped design the review. He contributed to interpretation of the analysis and to the draft of the final review, especially from a clinical perspective. Together with SW he will update the review.

DECLARATIONS OF INTEREST

Jan Verschuuren (JJGMV) has been involved in a thymectomy trial sponsored by the NIH, and in a FP7 European grant which involves testing a vaccine to treat AChR myasthenia gravis with Curavac. The Neurology department of the LUMC has received fees from BioMarin Ltd in 2009 to 2010, because of consultancies by JJGMV in the field of Lambert-Eaton myasthenic syndrome. JJGMV did not receive any personal payments. He has no known conflict of interest related to this review.

From 2008 to 2010 Stephanie Weinreich worked at the Erasmus MC Medical Center on a project funded through the Top Institute Pharma, Leiden, The Netherlands. Project partners were a public-private consortium including two pharmaceutical companies. The research concerned newborn screening for Pompe disease; this is unrelated to the Cochrane review at hand. She has no known conflict of interest related to this review.

Rob Scholten: none known.

Angeli van der Zwaag: none known.

Charlotte Vrinten: none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- ZonMw, the Netherlands Organisation for Health Research and Development, Netherlands.

CV and SW were paid by a ZonMw grant (project number 152002030)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed the title of the review protocol to clarify the content. The protocol was originally titled 'Ephedrine for myasthenia gravis'.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic Agents [*therapeutic use]; Cholinesterase Inhibitors [therapeutic use]; Ephedrine [*therapeutic use]; Myasthenia Gravis [*drug therapy]; Myasthenia Gravis, Neonatal [drug therapy]; Myasthenic Syndromes, Congenital [drug therapy]

MeSH check words

Adult; Child; Humans; Infant, Newborn